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Neurofibromatosis type 1 and McCune–Albright syndrome occurring in the same patient

J.GONZALEZ-MARTIN, S.GLOVER, S.DIXON,* A.FRYER,† H.CARTY,‡ C.SMITH,* S.B.KAYE AND J.VERBOV§

*Departments of Ophthalmology, *Paediatric Endocrinology, †Medical Genetics, ‡Radiology and §Dermatology, Royal Liverpool Children's Hospital (Alder Hey), Eaton Road, Liverpool L12 2AP, U.K.*

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Summary A patient with both neurofibromatosis type 1 (NF-1) and McCune–Albright syndrome is described. NF-1 and McCune–Albright are separate entities and this is the first report of a patient with clear evidence of both conditions.

Key words: McCune–Albright syndrome, neurofibromatosis type 1

We describe an unusual patient with features of both neurofibromatosis type 1 (NF-1) and McCune–Albright syndrome.

Case report

A female child born at term weighing 7 lb 10 oz (3460 g) was noted to have café-au-lait pigmentation on the buttocks, which increased in area over the first 3 weeks of life. By 5 months of age she had extensive, confluent café-au-lait pigmentation over both legs and the front and back of the trunk. The pigmentation stopped in the mid-line on the lower part of the abdomen (Fig. 1). There was one small café-au-lait patch on the left parietal area of the scalp. Her father had classical signs of NF-1 with multiple café-au-lait patches, Lisch nodules, cutaneous neurofibromas and axillary freckling. The appearance of the pigmentation in the child was more reminiscent of McCune–Albright syndrome but in view of NF-1 in her father, it was felt more likely that this represented an unusual manifestation of NF-1. A skeletal survey at 6 months of age showed no changes of fibrous dysplasia. She had two older siblings, neither of whom had any signs of neurofibromatosis but one had a port-wine stain on her right arm. Subsequently, a younger male sibling was born who presented at 1 week of age with facial asymmetry, unilateral congenital glaucoma and localized hypertrophy of the left side of the face. He developed signs of NF-1, with a number of small café-au-lait patches being apparent at 3 months of age. Magnetic resonance imaging (MRI) of his brain and

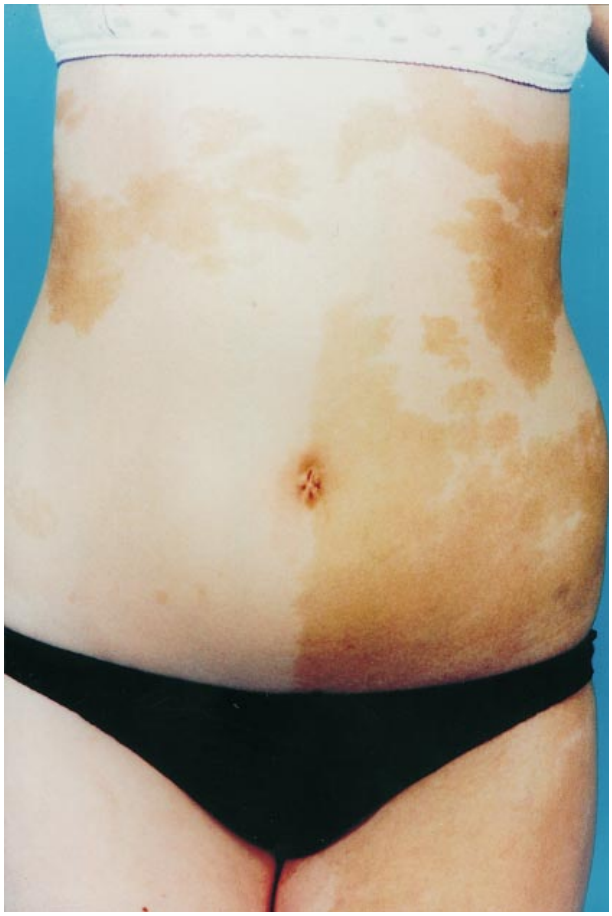

Figure 1. The patient at age 6 years. Extensive and confluent café-au-lait pigmentation is evident, which does not cross the mid-line over the lower abdomen.

orbits demonstrated the presence of an arachnoid cyst in the left temporal fossa producing hypoplasia of the adjacent temporal lobe and forward bowing of the lateral margin of the left orbit with proptosis of the globe.

At 6 years of age our patient presented with apparent haematuria, later recognized to be vaginal bleeding, a 6-month history of breast enlargement and a 12-month history of a rapid increase in height and weight. Both of these parameters were above the 90th centile. She showed pubertal changes: Tanner breast stage 3, pubic hair stage 1 and axillary hair stage 1. An examination under anaesthesia showed blood coming from the cervix. A localized tumour was excluded but an enlarged right ovary was demonstrated.

Pelvic ultrasound showed an enlarged uterus with thick endometrium and a large right ovary with solid and cystic components; the left ovary was normal. X-ray and MRI of the skull showed the presence of a left optic nerve glioma, an enlarged chiasm and hypothalamus, and thickening of the sphenoid (Fig. 2a,b) and occipital bone diploid space in keeping with fibrous dysplasia of the skull vault. The left hand and femur (Fig. 3a,b) showed fibrous dysplasia and increased skeletal maturity consistent with polyostotic fibrous dysplasia. Tanner and Whitehouse bone age X-ray demonstrated an advance of 0·8 years beyond chronological age. Basal luteinizing hormone, follicle-stimulating hormone and oestradiol levels were undetectable and the gonadotrophins showed no response to stimulation with luteinizing hormone-releasing hormone, in keeping with gonadotrophin-independent precocious puberty. Thyroid function tests were normal. There had been no change in her pigmentation and she had normal psychomotor development.

Ocular examination showed a best corrected visual acuity (BCVA) of 6/12 in both eyes, prominent corneal nerves, Lisch nodules, a normal-appearing optic disc and full visual fields. The clinical findings thus suggested that the patient had both NF-1 and McCune–Albright syndrome.

The family underwent genetic analysis for NF-1. Linkage analysis using three polymorphisms within the NF-1 gene (27 Alu, 127CA and 138CA)[1] and a very close flanking polymorphism detected by the marker D17S1824 showed that she had inherited the same

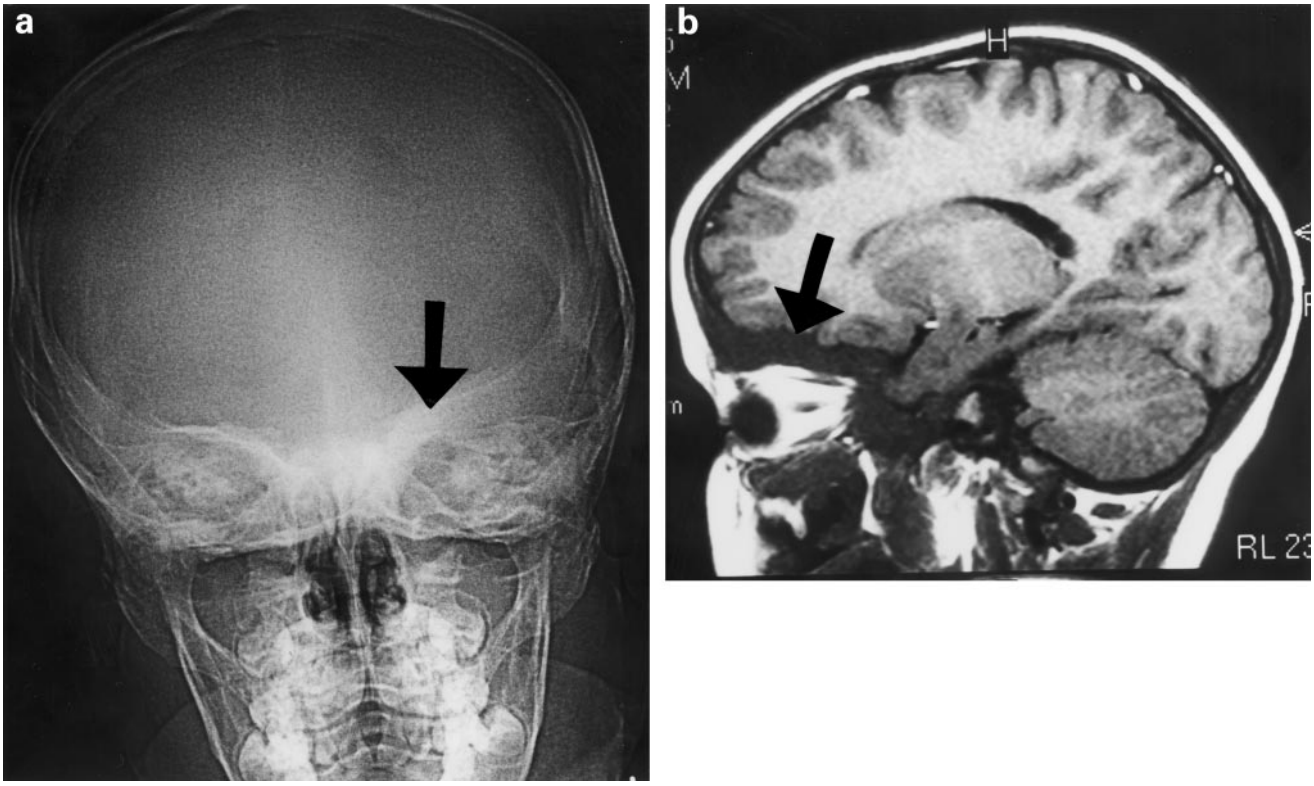

Figure 2. (a) Anterior–posterior view skull X-ray. Note the thickening of the sphenoidal wing on the left extending medially into the body of the sphenoid, typical appearances of fibrous dysplasia. (b) Magnetic resonance imaging scan. Sagittal T1 image of the brain. Note thickening of the diploid space and the sphenoid bone extending over the upper portion of the right orbit and into the body of the sphenoid.

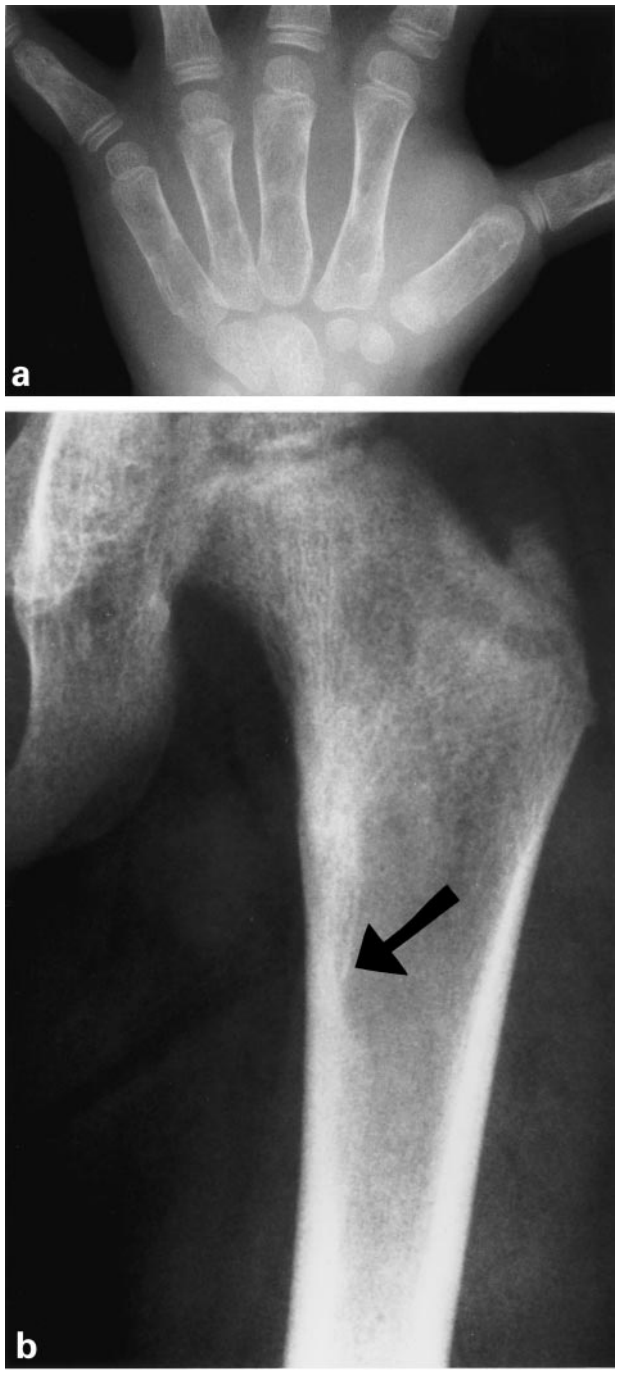

Figure 3. (a) X-ray of the left hand. The third metacarpal bone is wider and poorly modelled relative to the second and fourth; there is poor trabeculation and a ground glass appearance in it and in the little finger metacarpal in particular. These are changes of fibrous dysplasia. (b) X-ray of the left femur. The bone is generally osteopenic, and there is subtle change in the subtrochanter region of the femoral shaft with loss of the normal trabecular pattern centrally and early endosteal scalloping medially (arrow). Early stress lines are developing above the area of lucency.

paternal haplotype as her affected younger brother, thus supporting the diagnosis of NF-1. Lymphocyte DNA was also used to search for activating mutations within the guanine nucleotide-binding protein, α-stimulating activity polypeptide 1 (GNAS1) gene, which are known to cause McCune–Albright syndrome. Polymerase chain reaction and direct sequencing of a 163-bp product failed, however, to demonstrate either the Arg to His or Arg to Cys mutations at position 201, which have been reported in this syndrome.[2,3]

One year later, pubertal progression and vaginal bleeding had been halted by treatment with the antiandrogen cyproterone acetate. Following subsequent acceleration of linear growth, further breast development and vaginal bleeding, she was commenced on the aromatase inhibitor testolactone in gradually increasing doses to reduce known side-effects (abdominal cramps and loose stools) and a further arrest of pubertal progression was achieved. With conservative management of the optic nerve glioma the BCVA and visual fields remained unchanged.

Discussion

In 1936, McCune presented a case of osteitis fibrosa cystica, precocious puberty, multiple pigmentation of the skin and hyperparathyroidism in a 9-year-old girl.[4] The following year, Albright *et al.* described a triad of polyostotic fibrous dysplasia, skin pigmentation and precocious puberty in females.[5] In McCune–Albright syndrome there are usually fewer than six areas of light to dark brown cutaneous pigmentation with jagged edges of variable size.[6] As was apparent in our patient, they typically affect the forehead, nuchal, sacral, buttock or thigh areas and often stop at the mid-line. Although axillary freckling and neurofibromas were absent in our patient, this may in part be due to her age and may develop as she grows older.

Bone involvement is seen radiologically as a multilocular appearance beneath a thinned cortex, with areas of thickened bone and fibrosis, as seen in the skull, metacarpal bones and femur of our patient. Although fractures are common, bone changes can be clinically silent and may be preceded by precocious puberty. Ovaries show multiple cysts, and levels of oestradiol may correlate with the cyst size. There may be autonomous hyperfunction and increased sensitivity of other peripheral endocrine glands.

Precocious puberty has been reported in association with NF-1 in the presence[7] or absence[8,9] of optic pathway gliomas (in particular optic chiasmal gliomas)

and also in the presence of hypothalamic hamartomas.[10] Therefore, it could be considered that this case merely represents NF-1 presenting with a McCune–Albright syndrome phenotype, in the absence of genetic confirmation for McCune–Albright syndrome. What makes the case different from NF-1 alone are the osseous lesions with typical changes of fibrous dysplasia in the femur and metacarpal bones that have progressed over time, which is characteristic of McCune–Albright syndrome. In addition, the striking and unusual mid-line border of the pigmented cutaneous lesions suggests a mosaic condition such as McCune–Albright syndrome.

McCune–Albright syndrome is caused by a somatic mutation of the GNAS1 gene that encodes the α subunit of the G-protein, leading to overactivity of adenyl cyclase.[11] The activity of hormone-sensitive adenylate cyclase is regulated by at least two nucleotide-binding proteins, one stimulatory (Gs) and one inhibitory (Gi). Each is a heterotrimer with a unique α chain but identical polypeptides in the β and γ chains. The guanosine triphosphate-binding protein Gs couples hormone-receptor binding to adenyl cyclase activation. An early somatic mutation of the Gs α gene and the expression of an activated Gs protein in multiple tissues results in an inherited deficiency of Gs, which is associated with multiple phenotypic abnormalities, including generalized hormone resistance.[2]

The genetic analysis in our patient did not show either of the published activating mutations in the GNAS1 gene. This was not surprising, as the mosaic inheritance pattern would make it more likely that these would be found in the tissues affected by the disease, such as bones, with fibrous dysplasia, rather than in lymphocytic DNA.

Although there have been reports[12,13] suggesting that both McCune–Albright syndrome and NF-1 may coexist, the evidence has not been convincing. To our knowledge, this is the first report of clear clinical evidence of both conditions supported (at least for NF-1) using molecular genetics. Although there has been some doubt whether NF-1 and McCune–Albright syndrome are separate entities,[13] it is now clear that they are due to mutations in different genes.

The presentation of our patient's brother with congenital glaucoma as a neonate, in the absence of other features of NF-1, is also of interest; to our knowledge there has been only one previous report of a patient with NF-1 presenting as congenital glaucoma.[14]

References

1 Marchuk DA, Saulino AM, Tavakkol R *et al.* cDNA cloning of the type 1 neurofibromatosis gene: complete sequence of the NF1 gene product. *Genomics* 1991; **11**: 931–40.

2 Weinstein LS, Shenker A, Gejman PV *et al.* Activating mutations of the stimulatory G protein in the McCune–Albright syndrome. *N Engl J Med* 1991; **12**: 1688–95.

3 Shenker A, Weinstein LS, Moran A *et al.* Severe endocrine and nonendocrine manifestations of the McCune–Albright syndrome associated with activating mutations of the stimulatory G protein Gs. *J Pediatr* 1993; **123**: 509–18.

4 McCune DJ. Osteitis fibrosa cystica; the case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. *Am J Dis Child* 1936; **52**: 743–4.

5 Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of hyperpigmentation and endocrine dysfunction, with precocious puberty in females: report of five cases. *N Engl J Med* 1937; **216**: 727–46.

6 Landau M, Krafchik BR. The diagnostic value of café-au-lait macules. *J Am Acad Dermatol* 1999; **40**: 877–90.

7 Habiby R, Silverman B, Listernick R, Charrow J. Neurofibromatosis type I and precocious puberty: beyond the chiasm. *J Pediatr* 1997; **131**: 786–7.

8 Zacharin M. Precocious puberty in two children with neurofibromatosis type I in the absence of optic chiasmal glioma. *J Pediatr* 1997; **130**: 15–17.

9 Carmi D, Shohat M, Metzker A, Dickerman Z. Growth, puberty, and endocrine functions in patients with sporadic or familial neurofibromatosis type 1: a longitudinal study. *Pediatrics* 1999; **103**: 1257–62.

10 Biswas K, Kapoor A, Jain S, Ammini AC. Hypothalamic hamartoma as a cause of precocious puberty in neurofibromatosis type 1: patient report. *J Pediatr Endocrinol Metab* 2000; **13**: 433–4.

11 Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenyl cyclase in McCune–Albright syndrome. *Proc Natl Acad Sci USA* 1992; **89**: 5152–6.

12 Bachmann Andersen L, Sorensen SA. Diagnosis of von Recklinghausen neurofibromatosis and the Albright syndrome. Two case reports. *Neurofibromatosis* 1988; **1**: 120–3.

13 Riccardi VM. Neurofibromatosis and Albright's syndrome. *Dermatol Clin* 1987; **5**: 193–202.

14 Brownstein S, Little J. Ocular neurofibromatosis. *Ophthalmol* 1983; **90**: 1595–9.